422 Rec'd PCT/PTO 16 MAY 2000

FORM PTO-1390 (REV 1-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 146.1339

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/554772

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR98/02436	November 16, 1998	November 17, 1997

TITLE OF INVENTION: USE OF KETOLIDES FOR PREVENTING ARTERIAL THROMBOTIC COMPLICATIONS RELATED TO ATHEROSCLEROSIS

APPLICANT(S) FOR DO/EO/US: PETIT et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: French International Preliminary Examination Report

422 Rec'd PCT/PTO 16 MAY 2000

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/554772	PCT/FR98/02436	146.1339

17. [x] The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1070.00	$ 970.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $930.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $790.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $720.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $98.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	-20 =		x $22.00	$
Independent claims	-3 =		x $82.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$

TOTAL OF ABOVE CALCULATIONS =	$ 970.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). +	$
SUBTOTAL =	$ 970.00
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$
TOTAL NATIONAL FEE =	$ 970.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$ 40.00
TOTAL FEES ENCLOSED =	$1010.00
Amount to be refunded:	$
charged:	$

a. [x] A check in the amount of $ 1010.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Bierman, Muserlian and Lucas
600 Third Avenue
New York, NY 10016

Charles A. Muserlian
SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Our Ref.: 146.1339

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
PCT/FR98/02436
Francis PETIT
Serial No.:
Filed: Concurrently Herewith
For: USE OF...ATHEROSCLEROSIS

PCT Date: November 16, 1998

600 Third Avenue
New York, NY 10016

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

Page 1, before line 1, insert

--This application is a 371 of PCT/FR98/02436 filed November 16, 1998.--

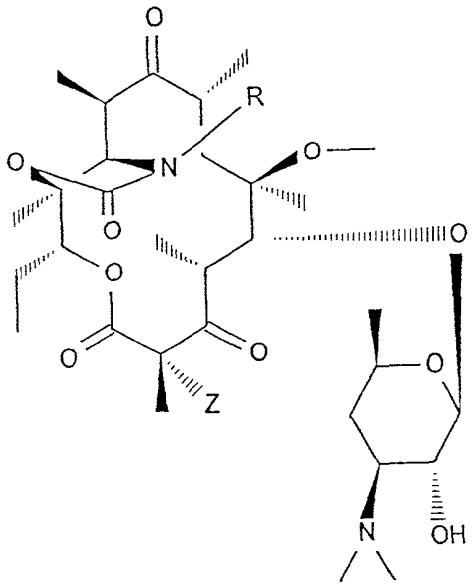
IN THE CLAIMS:

Cancel claims 1, 2 and 7 and add the following claims.

--8. A method of preventing arterial thrombotic complications associated with atherosclerosis in warm-blooded animals comprising administering to warm-blooded animals an effective amount of a

ketolide or its non-toxic, pharmaceutically acceptable acid addition salts sufficient to prevent arterial thrombotic complications associated with atherosclerosis.

9. The method of claim 8 wherein the ketolide has the formula



I

wherein R is $-(CH_2)_mO_n(X)YAr$, m and n are individually 0 or 1, X is selected from the group consisting of $-(NH_a)-$, $-CH_2-$ and $-SO_2-$, a is 0 or 1, Y is $-(CH_2)_b-(CH=CH)_c-(CH_2)_d-$, c is 0 or 1, $b + c + d \leq 8$, Z is hydrogen or halogen and Ar is unsubstituted or substituted aryl or heteroaryl.

Claim 3, cancel line 1 and insert --The method of claim 8 wherein the--.

Claims 4, 5 and 6, cancel line 1 of each and insert --The

method of claim 8 wherein--.

line 2 of each, cancel "in that".

10. The method of claim 8 wherein the ketolide is orally administered at 50 to 600 mg per day.--

REMARKS

The amendment is submitted to insert reference to the PCT application and to place the claims in proper method of use claims.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

Charles A. Muserlian, #19,683
Attorney for Applicant(s)
Tel. # (212) 661-8000

CAM:sd
Enclosure: Return Receipt Postcard

USE OF KETOLIDES FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS INTENDED FOR PREVENTING ARTERIAL THROMBOTIC COMPLICATIONS ASSOCIATED WITH ATHEROSCLEROSIS

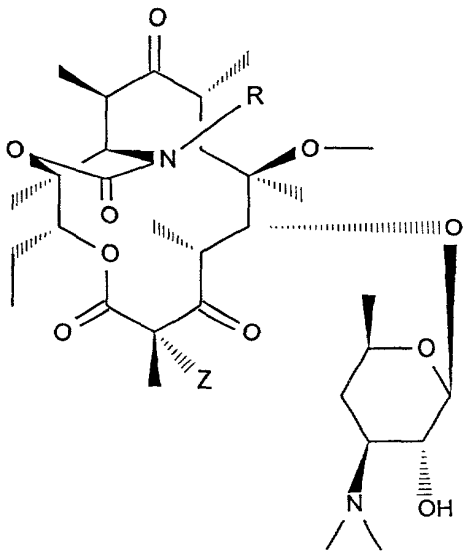
The present invention relates to a novel therapeutic application of ketolides.

The invention relates to the use of ketolides and pharmaceutically acceptable salts thereof for the preparation of pharmaceutical compositions intended for preventing arterial thrombotic complications associated with atherosclerosis.

The term "ketolide" refers to erythromycin derivatives lacking cladinose in position 3. These products have antibiotic properties (Antimicrobial Agents and Chemotherapy 1997, vol. 41, pp. 2149 to 2158, or 1997 vol. 41, pp. 454 to 459 or Lettre de l'infectiologue 1997, vol. 12, pp. 46 to 54).

Ketolides are also described, for example, in European Patents 0487411, 596802, 606024, 614905, 676409, 680967 and 799833 and International Patent Application WO 98/25942.

Among the preferred ketolides of the invention, mention may be made of the compounds of the formula (I) :



(I)

in which R represents a radical

$(CH_2)_mO_n(X)YAr$

in which m represents the number 0 or 1,

n represents the number 0 or 1,

X represents a radical $(NH)_a$, CH_2 or SO_2 with a representing the number 0 or 1,

Y represents a radical $(CH_2)_b-(CH=CH)_c-(CH_2)_d$ with c = 0 or 1 and b + c + d ≤ 8,

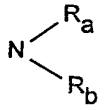
Z represents a hydrogen or halogen atom,

Ar represents an optionally substituted aryl or heteroaryl radical.

The aryl radical can be a phenyl or naphthyl radical.

The substituted or unsubstituted heterocyclic radical can be a thienyl, furyl, pyrrolyl, thiazolyl or oxazolyl radical, an imidazolyl radical, for example a 4-(3-pyridyl)-1H-imidazolyl radical, a thiadiazolyl, pyrazolyl or isopyrazolyl radical, a pyridyl, pyrimidyl, pyridazinyl or pyrazinyl radical, or alternatively an indolyl, benzofuryl, benzothiazyl or quinolyl radical.

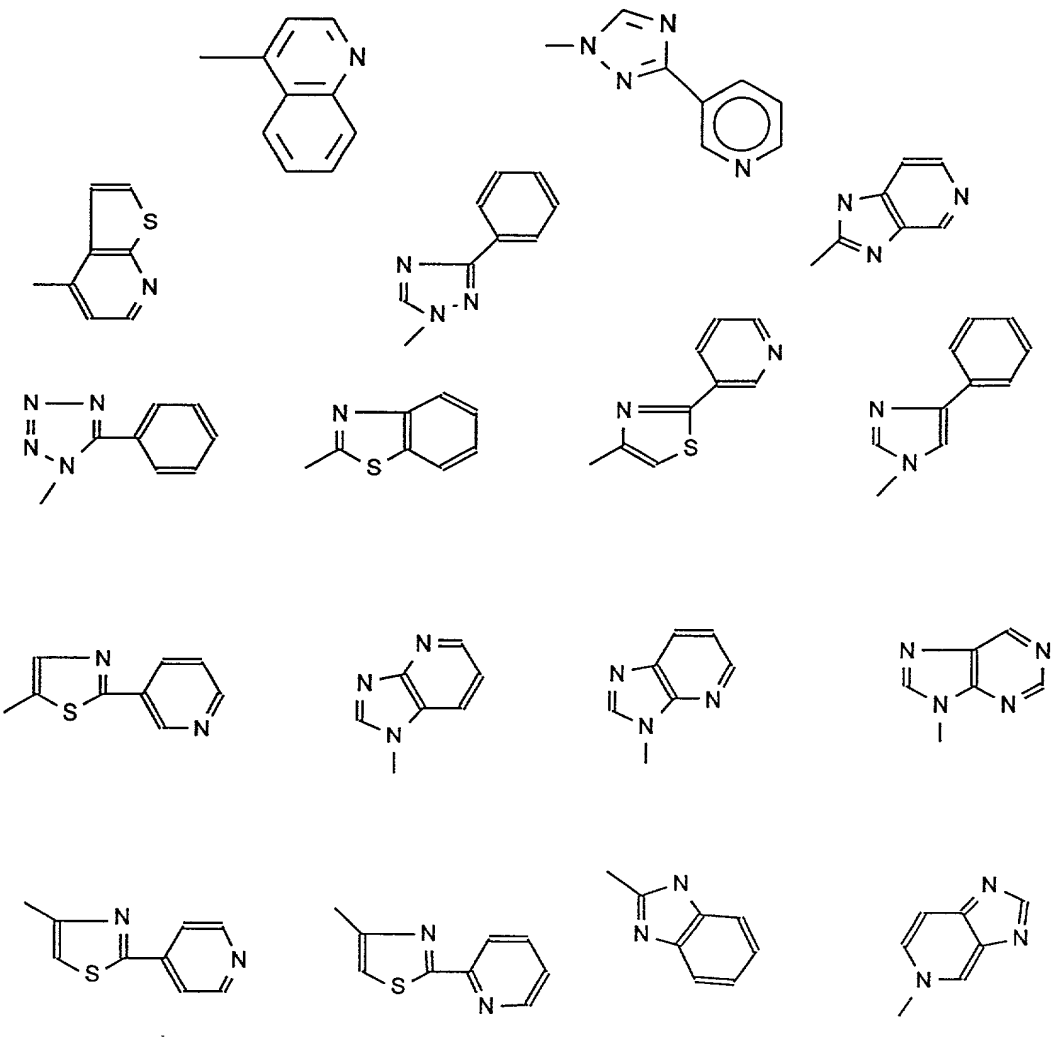
These aryl radicals can contain one or more groups chosen from the group consisting of hydroxyl radicals, halogen atoms, NO_2 radicals, CN radicals, alkyl, alkenyl or alkynyl radicals, O-alkyl, O-alkenyl or O-alkynyl radicals, S-alkyl, S-alkenyl or S-alkynyl radicals and N-alkyl, N-alkenyl or N-alkynyl radicals, containing up to 12 carbon atoms optionally substituted by one or more halogen atoms, the radical

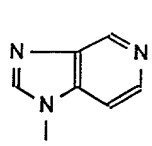
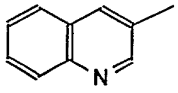
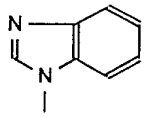
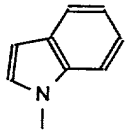
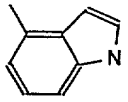
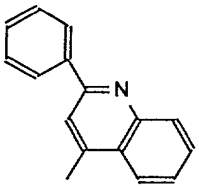
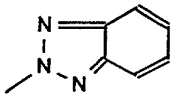
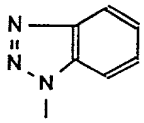
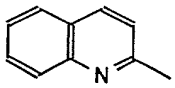
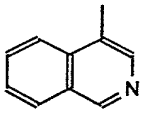
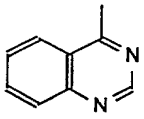
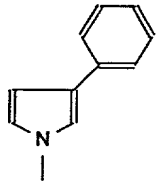
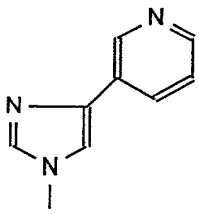
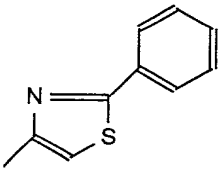
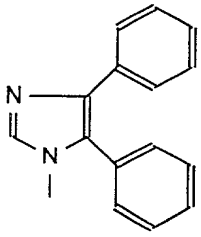
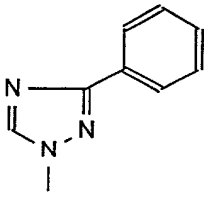
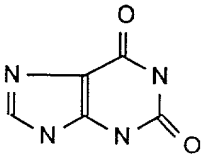
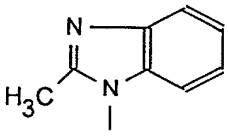
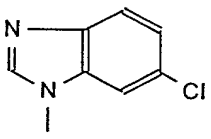
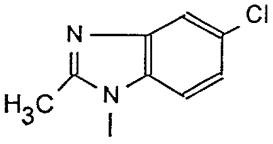


, where Ra and Rb, which may be identical or different, represent a hydrogen atom or an alkyl radical containing up to 12 carbon atoms, the radical

O
‖
-C-R_3, where R_3 represents an alkyl radical containing up to 12 carbon atoms, or an optionally substituted aryl or heteroaryl radical, where the aryl, O-aryl or S-aryl carboxylic or aryl, O-aryl or S-aryl heterocyclic 5- or 6-membered radicals comprise one or more heteroatoms, optionally substituted by one or more of the substituents mentioned below.

Preferred heterocycles which may be mentioned are, inter alia,



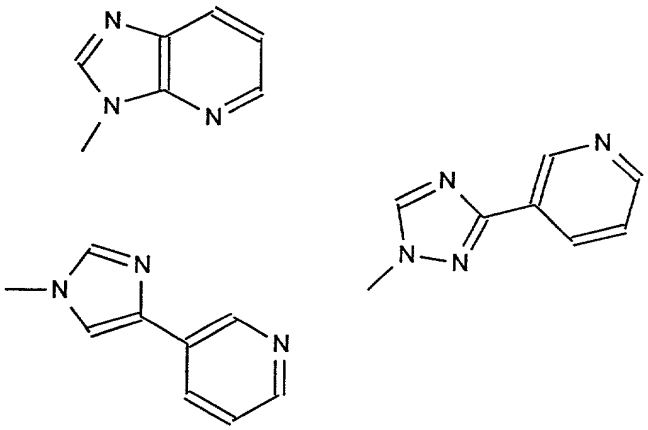





















and the heterocyclic radicals envisaged in European Patent Applications 487411, 596802, 676409 and 680967. These preferred heterocyclic radicals can be substituted by one or more functional groups.

Hal preferably represents a fluorine, chlorine or bromine atom.

Among the addition salts with acids which may be mentioned are the salts formed with acetic acid, propionic acid, trifluoroacetic acid, malic acid, tartaric acid, methanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid and, especially, stearic acid, ethylsuccinic acid or laurylsulphonic acid.

The aryl radical is preferably a heterocyclic aryl radical. Among the preferred ketolides which may be mentioned are the compounds in which Ar represents a radical



Among the preferred compounds of the invention which may be mentioned are the compounds of formula (I) whose names are given below : 11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-

3-O-methyl-alpha-L-ribohexopyranosyl)oxy]-6-O-methyl-3-oxo-12,11-([oxycarbonyl [[[2-[4-(3-pyridyl)-1H-imidazol-1-yl]-ethoxy]methyl]imino]]erythromycin (compound P) described in Patent Application WO 98/25942 in Example 2 or 11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexo-pyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(3-(3-pyridyl)-1H-1,2,4-triazol-1-yl)butyl)imino)erythromycin (compound P_1) described in Patent EP 680967 in Example 35, or **11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-2-fluoro-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridyl)-1H-imidazol-1-yl)butyl)-imino))erythromycin (A isomer)** (compound P_2) described in Patent EP 799833 in Example 3, or **11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridyl)-1H-imidazol-1-yl)butyl)imino))erythromycin** (compound P_3) described in Patent EP 680967 in Example 34.

Among the ketolides which are particularly advantageous, mention may be made of the products in European Patents 676409, 680967 and 799833.

The ketolides exhibit an anti-platelet-aggregating and antithrombotic activity, as shown by the results obtained in the experimental section disclosed below.

The invention thus relates to pharmaceutical compositions intended for preventing arterial complications, such as cerebrovascular accidents, myocardial infarction and unstable angina following atherosclerosis.

The infectious agent Clamydia pneumoniae appears to play a role in the development of atherosclerosis in man.

The ketolides are active against Clamydia pneumoniae.

As a result, the anti-infectious properties against Clamydia pneumoniae which are associated with their anti-platelet-aggregating activity allow them to be used to combat the development of atherosclerosis and thrombotic complications.

The invention also relates to pharmaceutical compositions containing a ketolide defined above which are intended for preventing arterial thrombotic complications associated with atherosclerosis.

These compositions can be administered orally, rectally, parenterally or locally by topical application to the skin and mucous membranes, but the route of administration is the oral route.

They can be solid or liquid and can be in the pharmaceutical forms commonly used in human medicine, such as, for example, simple or sugar-coated tablets, gel capsules, granules, suppositories, injectable preparations, ointments, creams or gels; they are prepared by the usual methods. The active principle(s) may be incorporated therein with excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or plant origin, paraffinic derivatives, glycols, various wetting, dispersing or emulsifying agents and preserving agents.

These compositions can also be in the form of a powder intended to be dissolved in a suitable vehicle, for example apyrogenic sterile water, at the time of use.

The dose administered is variable depending on the infection treated, the individual concerned, the route of administration and the product concerned. It can be, for example, between 50 and 600 mg per day via the oral route in an adult for the product P, P_1, P_2 or P_3.

PHARMACOLOGICAL STUDY

IN VITRO PLATELET AGGREGATION.

Principle

The platelet aggregation is measured by the turbidimetry method inspired by Born [1], by detecting the optical transmission through a platelet-rich plasma (PRP) to which and

aggregating agent has been added. When the platelets aggregate, the plasma becomes clear and the optical transmission increases.

Preparation of the platelet-rich plasma

Blood is taken (3 tubes per rabbit) by cardiac puncture from a rabbit into tubes containing sodium citrate. To obtain the platelet-rich plasma (PRP), the tubes are centrifuged at 160 g for 10 minutes. The supernatants are collected (PRP) and the pellet is re-centrifuged at 2000 g for 15 minutes to obtain the platelet-poor plasma (PPP). By dilution with the PPP, the PRP is adjusted to a concentration of 300,000 platelets per mm^3 ± 10%. The counting is carried out using a Coulter ZM counter.

Aggregation

Tubes containing 320 µl of PRP are incubated at +37°C for 30 minutes in pre-incubation wells.

The aggregometer is calibrated with the PPP for an optical transmission of 100% corresponding to a complete aggregation, and with the PRP obtained from the same rabbit for an optical transmission of 0% corresponding to the absence of aggregation.

The test product P is added in a volume of 40 µl. After incubation for 2 minutes, the aggregating agent (10 µM ADP, 0.2 mM sodium arachidonate or collagen 20 %g/ml) is added in a volume of 40 µl. The aggregation begins immediately and can be seen on the printer.

On the plot obtained, the height of the aggregation curve is measured in cm from the baseline before addition of the aggregating agent, and then converted into mVolts (=1/OD) using the formula 10 mV = 2.5 cm.

[1] - Born G.V.R., Aggregation of blood platelets by adenosine diphosphate and its reversal, Nature, 1962, 194, 927.

The results obtained are as follows:

Effect of product P on in vitro platelet aggregation - Comparison with aspirin.

% of inhibition of the aggregation induced by arachidonic acid +		
Concentrations	Product P *	Aspirin **
10^{-7} M	7	-
10^{-6} M	42	8
10^{-5} M	73	13
5 x 10^{-5} M	-	85
10^{-4} M	90	100

+ The rabbit platelets are placed in the presence of the product at different concentrations and the arachidonic acid is then added in a concentration of 0.2 mM.

* n = 2 rabbits

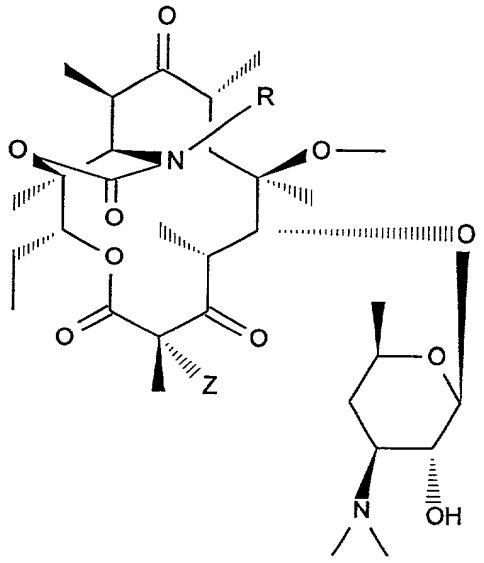
** n = 4 rabbits except for the concentration 5 x 10^{-5} M, where n = 2.

The preferred products P_1, P_2 and P_3 mentioned above also show good activity on this in vitro platelet aggregation test.

CLAIMS

1.- Use of ketolides and pharmaceutically acceptable salts thereof for the preparation of pharmaceutical compositions intended for preventing arterial thrombotic complications associated with atherosclerosis.

2.- Use according to Claim 1, characterized in that the ketolide corresponds to formula (I) :



(I)

in which R represents a radical

$$(CH_2)_mO_n(X)YAr$$

in which m represents the number 0 or 1,

n represents the number 0 or 1,

X represents a radical $(NH)_a$, CH_2 or SO_2 with a representing the number 0 or 1,

Y represents a radical $(CH_2)_b-(CH=CH)_c-(CH_2)_d$ with $c = 0$ or 1 and $b + c + d \leq 8$,

Z represents a hydrogen or halogen atom,

Ar represents an optionally substituted aryl or heteroaryl radical.

3.- Use according to Claim 1 or 2, characterized in that the ketolide is 11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy]-6-O-methyl-3-oxo-12,11-([oxycarbonyl [[[2-[4-(3-pyridyl)-1H-imidazol-1-yl]ethoxy]-methyl]imino]]erythromycin.

4.- Use according to any one of Claims 1 to 3, characterized in that the ketolide is 11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(3-(3-pyridyl)-1H-1,2,4-triazol-1-yl)butyl)imino)erythromycin.

5.- Use according to any one of Claims 1 to 3, characterized in that the ketolide is 11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-2-fluoro-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridyl)-1H-imidazol-1-yl)butyl)imino))erythromycin (A isomer).

6.- Use according to any one of Claims 1 to 3, characterized in that the ketolide is 11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridyl)-1H-imidazol-1-yl)butyl)imino))erythromycin.

7.- Use according to any one of Claims 1 to 6, characterized in that the ketolide is administered orally at a dose of between 50 and 600 mg per day.

ABSTRACT

The invention relates to a novel therapeutic application of ketolides. The invention relates to the use of ketolides for the preparation of pharmaceutical compositions intended for preventing arterial thrombotic complications associated with atherosclerosis.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (8-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing OR [ ] Declaration Submitted after Initial Filing

Attorney Docket Number	146.1339
First Named Inventor	Francis PETIT
COMPLETE IF KNOWN	
Application Number	PCT/FR98/02436
Filing Date	November 16, 1998
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

USE OF KETOLIDES FOR PREVENTING ARTERIAL THROMBOTIC COMPLICATIONS RELATED TO ATHEROSCLEROSIS

(Title of the Invention)

the specification of which

[ ] is attached hereto

OR

[X] was filed on (MM/DD/YYYY) 11/16/98 as United States Application Number or PCT International Application Number PCT/FR98/02436 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
97/14358 .	France	11/17/97	[ ]	[ ]	[X]
PCT/FR98/02436 PCT		11/16/98	[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box → [+]

PTO/SB/81 (9-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Bierman, Muserlian and Lucas	18,818	(4)	
Jordan B. Bierman	18,629		
Charles A. Muserlian	~~19,683~~		
Donald C. Lucas	31,275		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	Charles A. Muserlian				
Address	~~Bierman, Muserlian and Lucas~~				
Address	600 ~~Third Avenue~~				
City	~~New York~~	State	~~NY~~	ZIP	10016
Country	U.S.A.	Telephone	(212) 661-8000	Fax	(212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Francis		PETIT	

Inventor's Signature: [signature] Date: May 2, 2000

Residence: City	State	Country	Citizenship
Colombes FRX		France	France

Post Office Address: 111, rue Jules Ferry, F 92700 Colombes, France

Post Office Address:

City	State	Zip	Country
Colombes		F 92700	France

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

Please type a plus sign (+) inside the box → +

PTO/SB/01 (8-96)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:			☐ A petition has been filed for this unsigned inventor				
Given Name	Francoise	Middle Initial		Family Name	VACHERON	Suffix e.g. Jr.	
Inventor's Signature	Vacheron			Date	May 02, 2000		
Residence: City	Paris	State		Country	France	Citizenship	France
Post Office Address	54, Avenue Jean Jaures, F 75019 Paris, France						
Post Office Address							
City	Paris	State		Zip	F 75019	Country	Paris
Name of Additional Joint Inventor, if any:			☐ A petition has been filed for this unsigned inventor				
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature				Date			
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	
Name of Additional Joint Inventor, if any:			☐ A petition has been filed for this unsigned inventor				
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature				Date			
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	
Name of Additional Joint Inventor, if any:			☐ A petition has been filed for this unsigned inventor				
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature				Date			
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

☐ Additional inventors are being named on supplemental sheet(s) attached hereto